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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MOORE, WILLIAM W	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 05/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/735,056	KATZ ET AL.	
	Examiner	Art Unit	
	William W. Moore	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *57-62 and 72-84* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *57-62 and 72-84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed February 9, 2004, has been entered.

Response to Amendment

Applicant's accompanying submission filed on February 9, 2004, amends page 1 of the specification but erroneously indicates that Applicant's earliest priority document filed January 17, 1991, was U.S. patent application serial No. 08,642,734, when the correct application serial number is instead **07/**642,734. Applicant must correct the erroneous designation in response to this communication.

Applicant's submission of February 9, 2004, also cancels claims 63-71, adds a new claim 84, amends claims 57, 58, 60, and 83, and provides an Abstract, which is approved. The claim cancellations and entry of the new claim leaves claims 57-62 and 72-84 pending in the application. While the claim amendments address the rejection of record of claims 57-62 and 72-83 herein under 35 U.S.C. § 112, second paragraph, new grounds of rejection of the pending claims are stated herein under the first and second paragraphs of 35 U.S.C. § 112, as well as under the judicial doctrine of obviousness-type patenting, thus this communication is not made final.

Claim Objections

Claims 62 and 84 are objected to because of the following informalities: Claim 62 states two conjoined words "dehydrataseand" without punctuation or a space between

them. A comma, and then a space, should be introduced between the two words. Claim 84 states the possessive pronoun "its" in clause (4), then redundantly states "of the microorganism" in the same clause. The pronoun "its" should be replaced with the indefinite article "a". Appropriate correction is required.

Claims 57, 58, and 73 are objected to because they state, or in the case of claim 57 incorporate by dependency, improper Markush groups. "Compounds included within a Markush group [must] (1) share a common utility, and (2) share a substantial structural feature disclosed as being essential to that utility". See MPEP § 803.02. Yet claim 58 relates alterations of nucleic acid sequences encoding polypeptide domains that share no common utility and share no substantial structural feature and claim 73 relates disparate genera sharing no substantial structural feature in their chromosomes.

Specification

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: Claim 80 recites compounds not disclosed in the specification, specifically, the fourth through sixth compounds currently recited in claim 80 are not disclosed either in Tables 1 or in the text of the application as amended by incorporation of text and Examples present in application serial No. 07/642,734.

Election/Restrictions

The amendment filed on February 9, 2004, ostensibly cancels claims 63-71 drawn to a non-elected invention so as to present only claims drawn to an elected invention but this amendment is non-responsive (MPEP § 821.03). Claims 57, 58, 80, 82, and 83 specifically exceed the subject matters telephonically elected by Applicant on August 30, 2002, a restriction made final in the communication mailed June 2, 2003. Claims 72-79 and 81 depending from claim 57 also exceed the subject matters of the elected

Groups I and II, subject matters clearly indicated by the examiner in suggesting the clauses (3)(i) and (3)(ii) that now appear in claim 84. In response to this communication, Applicant is required to conform claim 57 to positively recite the elected alterations of polyketide synthase β-carbonyl processing functions – the inactivation or addition of β-ketoreductase, enoyltransferase, and dehydratase domains by altering a native polyketide synthase-encoding DNA sequence - and to delete from claim 58 the non-elected "enzymatic activities" of "acyl carrier protein, β-ketoacyl ACP synthase and acyltransferase", as well as to delete from claim 80 the compound 7-oxoerythromycin A and the six compounds at lines 4-6 of claim 80 which are not disclosed to result from a method of directing the biosynthesis of a polyketide analog requiring addition or inactivation of any or all of a β-ketoreductase, enoyltransferase, and dehydratase domain by altering a native polyketide synthase-encoding DNA sequence. In addition, because the activity of an acyltransferase domain is not involved in polyketide synthase β-carbonyl processing functions, Applicant is required to cancel claims 82 and 83 which describe polyketide analogs that the specification discloses to be prepared by one or more of DNA sequences encoding acyltransferase domains to genes encoding polyketide synthases.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 57-62, 72-75, 77-81, and 84 herein are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 5,824,513, made of record herewith. Although the conflicting claims are not identical, they are not patentably distinct from each other because methods of claims 57-62, 72-75, 77-81, and 84 herein for directing the biosynthesis of specific polyketide analogs embrace methods of the patented claims 1-11 and would improperly extend the "right to exclude" the public from subject matters of the patented claims 1-11.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 57-62, 76-78, and 82-84 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 57 describes methods for genetic manipulation of generic "polyketide biosynthetic gene-containing DNA sequence[s]" from any and all polyketide-producing microorganisms and claim 84 similarly describes methods for genetic manipulation of generic "DNA sequence[s] . . . encoding [ ] polyketide synthase polypeptide[s]" from any and all polyketide-producing microorganisms. However, the present specification, together with cumulative disclosure of specifications of Applicant's priority documents, describe no more than (1) the identification and manipulation of DNA sequences that encode *Saccharopolyspora erythraea* macrolide polyketide synthase [PKS] β-carbonyl processing domains (2) the identification of PKS domain-encoding regions for non-elected genetic manipulations in the *Streptomyces* species indicated at page 43 of the specification, including the acyltransferase domains of *S. hygroscopicus*, *S. caelestis*,

and *S. venezuelae* further discussed in several examples of the specification, and (3) a suggestion at page 44 of the specification that erythromycin-producing microorganisms in the genera *Saccharopolyspora*, *Streptomyces*, *Micromonospora*, and *Nocardia* have PKS genes suitable for disclosed genetic manipulations to direct the biosynthesis of erythromycin analogs. It is noted that Applicant amended the original specification of this application to include several examples and other text present only in Applicant's earliest priority document filed January 17, 1991, U.S. patent application serial No. 07/642,734, to provide disclosures of identification and manipulation of DNA sequences that encode the macrolide polyketide synthase [PKS] β-carbonyl processing domains of *Saccharopolyspora erythraea* in order to support claims drawn to practice of methods requiring the elected subject matters because the original specification had no corresponding disclosures. The specification is thus considered to provide an adequate written description of methods for directing the biosynthesis of erythromycin analogs through genetic manipulations which are Applicant's elected alterations of one or more β-carbonyl processing domain-encoding regions of PKS-encoding genes specifying the erythromycin polyketide synthases of microorganisms in the genera *Saccharopolyspora*, *Streptomyces*, *Nocardia*, and *Micromonospora*, four of seven genera recited in claim 73. Claims 58-62, 76-78, and 82 and 83 are included in this rejection because they depend from claim 57 and similarly exceed the written description of an elected subject matter provided by the present disclosure.

Claim 76 is independently unsupported by an adequate written description in the instant specification and specifications of Applicant's priority applications which, while they disclose intra-module modifications of one or more β-carbonyl processing domain-encoding regions of a *Saccharopolyspora erythraea* PKS gene according to the subject matter Applicant has elected, fail to exemplify, describe, discuss, or even suggest the

modification of any DNA sequence region of a *Saccharopolyspora hydroscopicus* PKS gene. Thus there is no basis whatsoever for the subject matter of claim 76.

Claim 80 is, in part, independently unsupported by an adequate written description in the instant specification and those of Applicant's priority applications because, while they disclose the preparation of seven of the erythromycin analogs recited in claim 80 - the first three recited at lines 2 and 3 of the claim and the final four recited at lines 5 and 6 of the claim - neither the instant specification nor those of the priority documents exemplify, describe, discuss, or even suggest the preparation of the three erythromycin compounds recited at lines 3 and 4 of claim 80. The preparation of the fourth through sixth compounds currently recited in claim 80 is simply not disclosed in the text or in Tables 1 of the instant application, nor in the applications serial Nos. 08/858,003 and 08/997,467, nor in the initial priority document, application serial No. 07/642,734.

Claims 82 and 83 are also independently unsupported by an adequate written description in the instant specification and those of Applicant's priority applications because there is no exemplification, description, discussion, or specific suggestion in any specification of the preparation of any particular rapamycin analog of claims 82 and 83 herein that corresponds to the elected subject matters, i.e., a rapamycin analog altered by DNA sequence alterations of a PKS gene to inactive a domain within a module, or to add a domain to a module, to alter its β-carbonyl processing function. "While one does not need to have carried out one's invention before filing a patent application, one does need to be able to describe that invention with particularity" to satisfy the description requirement of the first paragraph of 35 U.S.C. § 112. *Fiers v. Revel v. Sugano*, 25 USPQ2d 1601, 1605 (Fed. Cir. 1993). The specification provides no relevant identifying characteristics of a method of altering, by inactivating or adding, β-carbonyl processing domain-encoding regions of PKS-encoding genes other than

erythromycin PKS-encoding genes, and the specification discloses that microorganisms in only four genera among those recited in claim 73, *Streptomyces*, *Saccharopolyspora*, *Nocardia*, and *Micromonospora* have genes that encode a PKS supporting erythromycin biosynthesis. The specification likewise provides no relevant identifying characteristics of methods that permit alteration of any *Saccharopolyspora hydroscopicus* PKS gene of claim 76, that permit preparation of the fourth through sixth compounds recited in claim 80, or that permit preparation of any particular polyketide analog among the elected methods of claims 82 and 83. The specification's treatment of even the elected subject matters within the pending claims is considered to be entirely prospective where skilled artisans in the relevant field of polyketide biosynthesis could not predict the structure or organization of PKS genes, other than erythromycin PKS genes, to be altered according to the methods of claims 57-62, 76-78, and 82-84, or to provide the fourth through sixth compounds of claim 80.

Claims **57-62, 76-78, and 82-84** are rejected under 35 U.S.C. § 112, first paragraph, because the specification is not enabling for any embodiment of a directed biosynthesis of any and all "specific polyketide analog[s]" by isolation and manipulation of generic polyketide synthase-encoding genes wherein a β-carbonyl processing domain-encoding region is inactivated or added in any gene associated with polyketide biosynthesis in any conceivable microorganism identified as producing a polyketide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, make and use the invention commensurate in scope with these claims.

Claims 57 and 84 contemplate identification, isolation, mapping, and manipulation of great variety of polyketide biosynthetic genes - genes not limited in claim 57 to an integral PKS gene of the kind altered in the instant application and its priority documents - from any microorganism that produces any sort of polyketide where the manipulation, according to Applicant's August 30, 2002, election, is the inactivation or the addition of one or more β-carbonyl processing domain-encoding regions. Claims 57 and 84 further contemplate that the result of such manipulation will be the "biosynthesis of a specific

polyketide analog" where starter and/or extender units of any kind are included. Yet the specification and its priority documents teach only the identification and manipulation of PKS domains in integral, multi-module, PKS polypeptides conducting biosynthesis of the macrolide erthromycin. Indeed, neither the prior art made of record herewith, nor the present, amended, specification, identifies or teaches the structure of all of the diverse polyketides that are the product of microbial biosynthesis, with which the artisan may predict a set of specific analogs, or the nature of nucleic acid sequences encoding modules within a PKS polypeptide involved in their biosynthesis, polypeptides that need not in claim 57 have an integral amino acid sequence that comprises several chain-extending modules. Claims 58-62, 76-78, and 82 and 83 are included in this rejection because they depend from claim 57 and, like claim 57, exceed the scope of enablement provided by the present disclosure, even if taken with the prior art of record.

It is well settled that 35 U.S.C. § 112, first paragraph, requires that a disclosure be sufficiently enabling to allow one of skill in the art to practice the invention as claimed without undue experimentation and that unpredictability in an attempt to practice a claimed invention is a significant factor supporting a rejection under 35 U.S.C. §112, first paragraph, for non-enablement. See, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (recognizing and applying the "*Forman*" factors). Cf., *Ex parte Forman*, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986) (citing eight factors relevant to analysis of enablement). Applying the "*Forman*" factors discussed in *Wands*, ***supra***, to Applicant's disclosure, it is apparent that:

a) the specification lacks adequate, specific, guidance for genetic manipulation to alter the amino acid sequences of discontinuous polypeptides accepting any conceivable starter or extender units wherein one or more modules might be altered to direct the biosynthesis of any specific polyketide analog other than an erythromycin analog,

b) the specification lacks working examples wherein genes encoding integral, or discontinuous, polyketide synthase polypeptides beyond an erythromycin PKS

are altered to the extent recited in the claims to produce a specific polyketide analog,

c) in view of the prior art publications of record herein, the state of the art and level of skill in the art do not support such alteration, and,

d) unpredictability exists in the art where no members of other classes of PKS polypeptides have been altered to direct the biosynthesis of specific analogs of polyketides other than erythromycin.

Thus the scope of subject matters embraced by claims 57-62, 76-78, and 82-84 is unsupported by the present specification even if taken in combination with teachings available in the prior art.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 57-62 and 72-84 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant's amendment of clause 2 of claim 57 removes the inaccurate association of a polypeptide feature within the structure of a gene, a polynucleotide, yet clause 2 of the claim remains indefinite in reciting, "a sequence fragment encoding for polyketide synthase enzymatic activity", because genes do not encode "activities" but polypeptides and their constituent domains. Claim 57 is independently indefinite where clause (3) recites, "one or more specified changes [in a DNA] sequence fragment", because the claim nowhere "specifies" any particular changes, whether those elected by Applicant for prosecution nor any others. Claim 57 is further independently indefinite in reciting, in clause (4), "introducing said altered DNA sequence . . . to replace an original sequence" because the public and the artisan, attempting to determine the metes and bounds of the intended subject matter, cannot ascertain the nature of any particular "original" sequence where all nucleic acid sequences in the genome of a polyketide-producing organism would be "original". Claims 58-62 and 72-83 depending from claim 57 are

included in this rejection because they fail to correct one or more of these aspects of its indefinite description.

Claims 57 and 84 are independently indefinite in reciting "specific polyketide analog[s]" on their preambles because, apart from whether or not claim 57 conforms to a description of the nature of genetic alterations that Applicant elected, methods of claims 57 and 84 do not state a result that agrees with the preamble where the process steps do not indicate the production of "a" polyketide analog that is "specific". Claims 58-62, 72-79 and 81-83 depending from claim 57 are included in this rejection because they do not correct this aspect of its indefinite description.

Claim 77 is independently indefinite in reciting "and derivatives or analogs thereof" because claim 57, from which it depends, already describes a method for directing the biosynthesis of, i.e., producing, "specific polyketide analogs", thus claim 77 illogically describes specific analogs of some non-specific "derivative or analogs" and the public and the artisan, attempting to determine the metes and bounds of the intended subject matter, cannot ascertain the nature of the resulting method by its product. Claims 81 and 82 are independently rejected because they are indefinite in reciting, respectively, "protein" and "proteins" where Applicant intends, the disclosure requires, and claim 57 only provides antecedent basis for, a particular protein, a polyketide synthase, thus claims 81 and 82 cannot further limit the scope of the claim from which they depend.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is now 571.272.0933. The examiner can normally be reached between 9:00AM and 5:30PM

EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can now be reached at 571.272.0928. The fax phone numbers for all communications for the organization where this application or proceeding is assigned remains 703.872.9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is now 571.272.1600.

William W. Moore
May 14, 2004

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